Corlanor (Ivabradine), First HCN Channel Blocker, FDA Approved for the Treatment of Patients with Heart Failure

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Heart failure is a life-threatening condition that affects approximately 5.7 million individuals aged ≥20 years in the United States.[1] With an estimated 870,000 new cases of heart failure occurring annually, heart failure is expected to affect more than 8 million people aged ≥18 years by 2030—an alarming 46% increase from 2012.[1] And because heart failure increases in individuals aged ≥65 years, this disease will have a major impact in the coming decades as the aging US population increases steadily.[1]

Heart failure occurs when the heart cannot pump sufficient blood and oxygen.[2] Many patients with heart failure have a reduced left-ventricular ejection fraction (LVEF), also referred to as systolic heart failure.[3] A reduced LVEF indicates that the heart muscle does not contract effectively, and less oxygen-rich blood is pumped out to the body.[4] An elevated heart rate is associated with an increased mortality risk, cardiovascular (CV) mortality, and hospital admissions, particularly in patients with coronary artery disease (CAD) and left-ventricular dysfunction. Conversely, a reduced heart rate is associated with improved outcomes.[5]

The symptoms of heart failure include dyspnea, fatigue, edema, congestion and/or persistent cough, and a rapid or irregular heartbeat.[2,3] The majority of patients with heart failure have symptoms caused by impaired left-ventricular myocardial function.[3] The New York Heart Association (NYHA) Functional Classification system categorizes heart failure into 4 classes (I through IV) based on the severity of symptoms, ranging from mild (class I) to severe (class IV).[6]

Associated with a high rate of morbidity and mortality, heart failure caused 1 in 9 deaths in 2009.[7] Approximately 50% of patients with heart failure die within 5 years of diagnosis.[7] In addition to its poor prognosis and comorbid conditions, heart failure is associated with serious complications, including kidney damage or failure, arrhythmia, heart valve problems, and liver damage.[2] Overall, heart failure imposes a profound clinical and economic burden.[8]

Heart failure accounted for $31 billion in total annual US costs ($21 billion in direct costs, and nearly $10 billion in indirect costs) in 2012, with 80% of the direct costs attributed to hospitalization.[9] In fact, heart failure is the primary diagnosis in approximately 1 million hospitalizations annually and is the leading reason for hospitalizations in patients aged ≥65 years.[10,11]

Although the majority of heart failure hospitalizations include patients aged ≥65 years, hospitalizations for patients aged <65 years increased by 15% between 2000 and 2010.[10] Furthermore, more Medicare dollars are spent on heart failure than on any other diagnosis.[8] This rising costs trend for heart failure is expected to continue, with total direct medical costs projected to increase to $70 billion by 2030.[9]

Early diagnosis and treatment are essential to improving the quality and the duration of life, for patients with heart failure.[7] Timely and appropriate outpatient medical care can reduce or prevent hospitalizations for patients with heart failure.[10]

Nonpharmacologic approaches to managing heart failure include behavioral and dietary changes, appropriate physical activity, and daily symptom monitoring.[7] Pharmacologic treatments typically include a combination of medications, depending on the symptoms. These agents comprise renin-angiotensin system inhibitors, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers; beta-blockers; diuretics; aldosterone antagonists; inotropes; and digoxin.[2]

Ivabradine: A New Oral Option for Treating Heart Failure

On April 15, 2015, the US Food and Drug Administration (FDA) approved ivabradine (Corlanor; Amgen) to reduce the risk for hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with LVEF ≤35%, who are in sinus rhythm with a resting heart rate of ≥70 beats per minute (bpm) and are taking maximally tolerated doses of beta-blockers or have a contraindication to beta-blockers.[12,13] Ivabradine, an oral agent, is a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker.[12] Ivabradine is a first-in-class HCN channel blocker, and the first chronic heart failure medication to be approved by the FDA in nearly a decade.[13,14]

Table Ivabradine versus Placebo: Primary Composite End Point and Components from the SHIFT Study

End point	Ivabradine		Placebo		Hazard ratio	*P* value
	Patients, N (%) (N = 3241)	Annual incidence rate,[a] %	Patients, N (%) (N = 3264)	Annual incidence rate,[a] %		
Primary composite end point: time to first hospitalization for worsening heart failure or CV death[b]	793 (24.5)	14.5	937 (28.7)	17.7	0.82 (95% CI, 0.75-0.90)	<.001
Hospitalization for worsening heart failure	505 (15.6)	9.2	660 (20.2)	12.5		
CV death as first event	288 (8.9)	4.8	277 (8.5)	4.7		
Hospitalization for worsening heart failure[c]	514 (15.9)	9.4	672 (20.6)	12.7	0.74 (95% CI, 0.66-0.83)	
CV death[c]	449 (13.9)	7.5	491 (15.0)	8.3	0.91 (95% CI, 0.80-1.03)	

[a]Annual incidence rate = number of patient-years × 100.
[b]Patients who died on the same calendar day as their first hospitalization for worsening heart failure are counted under CV death.
[c]Analyses of the primary composite end points were not prospectively planned to be adjusted for multiplicity.
CI indicates confidence interval; CV, cardiovascular.
Source: Corlanor (ivabradine) prescribing information; April 2015.

Ivabradine was granted a priority review and a fast-track review by the FDA, based on its potential to treat a life-threatening condition and fill an unmet medical need.[13]

Norman Stockbridge, MD, PhD, Director of the FDA's Division of Cardiovascular and Renal Products, said, "Heart failure is a leading cause of death and disability in adults. Corlanor is thought to work by decreasing heart rate and represents the first approved product in this drug class."[13]

Jeffrey S. Borer, MD, Professor of Medicine, Cell Biology, Radiology and Surgery, and chief of Cardiovascular Medicine at State University of New York, Downstate Medical Center, commented, "The approval of Corlanor is an important step forward for the treatment of patients with chronic heart failure in the U.S. Because its mechanism of action is unique, it will complement the use of standard heart failure therapies, including beta-blockers."[14]

Mechanism of Action

Ivabradine blocks the HCN channel that is responsible for the cardiac pacemaker, which regulates the heart rate.[12] Ivabradine reduces the spontaneous pacemaker activity of the sinoatrial (cardiac sinus) node by selectively inhibiting the I_f current to slow the heart rate, with no effect on ventricular repolarization and no effect on myocardial contractility.[12]

Ivabradine causes a dose-dependent reduction in the heart rate. The size of the effect is dependent on the baseline heart rate (ie, a greater heart rate reduction occurs in patients with a higher baseline heart rate).[12]

Ivabradine is prescribed with a patient medication guide about its use and safety information.[13]

Dosing and Administration

The starting dose of ivabradine is 5 mg twice daily. After 2 weeks, the dose should be adjusted based on the patient's heart rate. The maximum dose of ivabradine is 7.5 mg twice daily. The recommended initial dose is 2.5 mg twice daily for patients with conduction defects and for patients whose bradycardia could lead to hemodynamic compromise.[12] Ivabradine is available in 5-mg and 7.5-mg tablets.[12]

Clinical Trials

The SHIFT Study

The SHIFT study was a randomized, double-blind clinical trial comparing ivabradine versus placebo in 6558 adults (mean age, 61 years) with stable NYHA class II to IV heart failure, LVEF ≤35%, and a resting heart rate ≥70 bpm.[5,12] The primary end point was a composite of the first hospitalization for worsening heart failure or for CV death. The median follow-up was 22.9 months.[5,12]

CAD was the underlying cause of chronic heart failure in 68% of the patients. Approximately 49% of patients had NYHA class II heart failure, 50% had NYHA class III heart failure, and 2% had NYHA class IV heart failure at baseline.[12] The mean LVEF was 29%. All patients started taking ivabradine 5 mg (or a matching

placebo) twice daily, and the dose was increased to 7.5 mg twice daily or decreased to 2.5 mg twice daily to maintain resting heart rate between 50 bpm and 60 bpm, as tolerated. The majority of patients in the SHIFT clinical trial were taking beta-blockers (89%), ACE inhibitors and/or angiotensin II antagonists (91%), diuretics (83%), and antialdosterone agents (60%).[12]

The results demonstrated that ivabradine reduced the risk for the combined end point of hospitalization for worsening heart failure and CV death based on a time-to-event analysis (**Table**).[12]

The treatment effect reflected only a reduction in the risk for hospitalization for worsening heart failure but did not reduce the mortality rate: ivabradine did not have significant benefit on CV death.[12] Patients who received ivabradine had an average reduction of 15 bpm in heart rate from a baseline value of 80 bpm.[5]

The SHIFT study investigators concluded that the findings "support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of heart failure."[5]

The BEAUTIFUL Study

The BEAUTIFUL study was a randomized, double-blind, placebo-controlled clinical trial of 10,917 patients with CAD, impaired left-ventricular systolic function (ejection fraction <40%), and a resting heart rate ≥60 bpm.[12,15] Patients had stable symptoms of heart failure and/or angina for at least 3 months, and they received conventional CV medications at stable doses for at least 1 month.[12] Patients were randomized in a 1:1 ratio to receive ivabradine or placebo at an initial dose of 5 mg twice daily with the dose increased to 7.5 mg twice daily, depending on the patient's resting heart rate and tolerability.[12,15]

The primary end point was the composite of time to first CV death, hospitalization for acute myocardial infarction, or hospitalization for new-onset or worsening heart failure.[12] The majority (61.4%) of patients had NYHA class II heart failure and 23.2% had class III heart failure; none of the patients had class IV heart failure.[12,15]

At a median follow-up of 19 months, ivabradine did not significantly affect the primary composite end point (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.91-1.10).[12,15]

The SIGNIFY Study

The SIGNIFY study was a randomized, double-blind clinical trial of 19,102 adults with stable CAD, but without clinically evident heart failure (NYHA class I).[12,16] Beta-blocker therapy was not required. The initial dose of ivabradine was 7.5 mg twice daily, and the dose could be increased up to 10 mg twice daily or downtitrated to 5.0 mg twice daily to achieve a target heart rate of 55 bpm to 60 bpm.[12]

The primary end point of this study was a composite of the first occurrence of CV death or myocardial infarction. At a median follow-up of 24.1 months, ivabradine did not significantly affect the primary composite end point (HR, 1.08; 95% CI, 0.96-1.20).[12,16]

Adverse Events

The most common adverse reactions occurring in ≥1% of patients who received ivabradine included bradycardia (10%), hypertension (8.9%), atrial fibrillation (8.3%), and luminous phenomena (2.8%).[5,12] The most common adverse events leading to the discontinuation of ivabradine treatment in the SHIFT clinical trial included atrial fibrillation (4%) and heart failure (2%).[5]

Contraindications

Ivabradine is contraindicated in patients with acute decompensated heart failure; blood pressure <90 mm Hg (systolic) and 50 mm Hg (diastolic); sick sinus syndrome, sinoatrial block, or third-degree atrioventricular block, unless a functioning demand pacemaker is present; resting heart rate <60 bpm before treatment with ivabradine; severe hepatic impairment; pacemaker dependence; and the concomitant use of strong cytochrome (CY) P450 3A4 inhibitors.[12]

Drug Interactions

CYP450-based interactions. Ivabradine is primarily metabolized by CYP3A4. The concomitant use of CYP3A4 inhibitors increases ivabradine plasma concentrations, and the use of CYP3A4 inducers decreases ivabradine plasma concentrations. Increased plasma concentrations may exacerbate bradycardia and conduction disturbances.[12]

Negative chronotropes. The majority of patients receiving ivabradine will also take a beta-blocker. The risk for bradycardia increases with the concomitant administration of drugs that slow the heart rate (eg, digoxin, amiodarone, beta-blockers). The heart rate should be monitored in patients taking ivabradine with other negative chronotropes.[12]

Pacemakers. Ivabradine dosing is based on heart rate reduction, targeting a heart rate of 50 bpm to 60 bpm. Ivabradine is not recommended in patients with demand pacemakers set to rates ≥60 bpm.[12]

Warnings and Precautions

Fetal toxicity. Ivabradine may cause fetal toxicity when administered to a pregnant woman, based on findings in animal studies.[12]

Atrial fibrillation. Ivabradine increases the risk for

atrial fibrillation. Cardiac rhythm should be monitored regularly. Ivabradine should be discontinued if atrial fibrillation develops.[12]

Bradycardia and conduction disturbances. Bradycardia, sinus arrest, and heart block have occurred with ivabradine therapy.[12] The concurrent use of verapamil or diltiazem will increase ivabradine exposure, may contribute to heart-rate lowering, and should be avoided. Ivabradine should not be used in patients with second-degree atrioventricular block, unless a functioning demand pacemaker is present.[12]

Use in Specific Populations

Pregnancy. Ivabradine may cause fetal harm when administered to a pregnant woman.[12]

Lactation. Because of the potential risk to breast-fed infants from exposure to ivabradine, breast-feeding is not recommended in patients receiving ivabradine.[12]

Females and males of reproductive potential. Ivabradine may cause fetal harm; females of reproductive potential should be advised to use effective contraception during treatment with ivabradine.[12]

Pediatric use. The safety and effectiveness of ivabradine in pediatric patients have not been established.[12]

Geriatric use. No pharmacokinetic differences have been observed in elderly (aged ≥ 65 years) or very elderly (aged ≥75 years) patients compared with the overall population; however, ivabradine has only been studied in a limited number of patients aged ≥75 years.[12]

Hepatic impairment. No dosage adjustment is required for patients with mild or moderate hepatic impairment.[12]

Renal impairment. No dosage adjustment is required for patients with creatinine clearance 15 mL/min to 60 mL/min.[12] No data are available for patients with creatinine clearance <15 mL/min.[12]

Conclusion

The FDA approval of ivabradine added a new treatment option for patients with heart failure—the first oral HCN channel blocker. When added to guideline-based treatment, ivabradine demonstrated a significant reduction in the major risks associated with heart failure compared with placebo, including an 18% relative risk reduction in first hospitalization for worsening heart failure or CV death (primary composite end point) in the SHIFT clinical trial. The treatment effect reflected only a reduction in the hospitalization risk for worsening heart failure; it did not show a favorable effect on the mortality component of the primary end point. The findings from the SHIFT clinical trial underscore the relevant role of targeting heart rate in the treatment of patients with heart failure. ■

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